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Description

SUMMARY OF THE INVENTION

This invention is concerned with a sustained release oral dosage form for medicaments wherein the dosage form has approximate zero-order release characteristics, whereby plasma levels of the medicament tend to remain largely constant for an appropriate time. The dosage form comprises a coated matrix of the medicament in a cellulosic gelling agent. The coating consists of ethyl cellulose which provides an initial delay before main release of medicament. The formulation of this invention may also contain a buffer to maintain the release rate of an acidic or basic drug independent of pH as the dosage form moves through the alimentary canal.

BACKGROUND OF THE INVENTION

Oral dosage forms for the sustained release of drugs from water insoluble and slowly soluble matrices are well known in the prior art such as U.S. Patent 4,389,393 and the release is known to occur by a diffusion process. As the diffusion path length increases with time, a linear plot of percent released versus $t^{1/2}$ is obtained which is not ideal for maintenance of a plasma level which is intended to be more or less constant for an appropriate time.

Similarly, matrix systems usually exhibit an initial rapid release (the "burst" effect) of active ingredient which promotes increased plasma levels and may cause the adverse reactions which the dosage form was designed to minimize.

US Patent Nos. 4,505,890 and 4,610,870 describe controlled release formulations having a core containing gelling agent and a coat comprising either a film-forming agent and plasticizer or a hydrophilic polymer and a hydrophobic polymer. However in those formulations, the core contains either from 8 - 14%, or from 5 - 15% of gelling agent.

GB-A-2151921 provides a controlled release tablet for oral administration of ketoprofen, which comprises ketoprofen in a hydrophilic matrix, such as hydroxyethylcellulose, covered with a gastro-resistant coating, preferably cellulose acetophthalate.

With the present invention the "burst" effect has been eliminated by providing the matrix with a coating material that provides an additional barrier to diffusion of water into the matrix and drug solution out of the matrix to the external environment.

DETAILED DESCRIPTION OF THE INVENTION

The invention provides a sustained release pharmaceutical composition in oral dosage form which comprises: (1) a core matrix containing at least 20% of a derivatized cellulosic gelling agent, a medicament homogeneously dispersed therein and optionally pharmaceutically acceptable excipients; and (2) a coating layer surrounding the core matrix; characterised in that the material used for the coating layer is ethylcellulose.

The derivatized cellulosic gelling agents useful as the core matrix in the novel dosage form of this invention include: methylcellulose, such as Methocel^{R} A4M (Dow Chemical Co.); hydroxypropylmethylcellulose, (HPMC) such as Methocel^{R} E4M, F4M, or K4M (Dow Chemical Co.); or hydroxypropyl-cellulose (HPC).

The preferred polymer for use as the matrix is a hydroxypropylmethylcellulose, especially with a viscosity of about 400 $kgm^{-1}s^{-1}$ (4000 centipoises), for example Methocel^{R} K4M.

The ethylcellulose coating layer does not contain any medicament. It is preferably applied as a dispersion.

Examples of drugs useful in the novel formulations are (+)-trans-1a,2,3,4a,5,6-hexahydro-9-hydroxy-4-(1-propyl)-4H-naphth[1,2-b]-1,4-oxazine, enalapril, amitriptyline, cyproheptadine, cyclobenzoprine, timolol, propranolol, betaxolol, indomethacin, sulindac, diflunisal, ibuprofen, and norfloxacin.

The medicaments useful in the novel formulation of this invention may be weak bases, such as primary or secondary amines, or weak acids, such as carboxylic acids and their salts. The salts of the weak bases are preferably acid addition salts with strong acids such as hydrochloric, hydrobromic, phosphoric, sulfuric or maleic acid. The salts of the carboxylic acids are normally sodium or potassium salts. Where appropriate the active ingredient may be in zwitterionic form e.g. as an internal salt or betaine.

Medicaments which are weak acids or bases and their salts display an aqueous solubility that in most cases is dependent on the pH of the aqueous environment. Thus as the pH of the gastrointestinal tract

varies from 1 to 7.5, the solubility of the medicament and consequently its release from the prior art dosage forms will vary depending upon its position in the alimentary canal and time after administration.

In a further aspect of this invention, the pH dependent release is eliminated by including a buffer in the core matrix. This produces a microenvironment of constant pH whereby the solubility of the drug is unchanged regardless of the pH of the body fluids of the external environment.

Buffering agents useful with the salts of basic drugs include, for example, citric acid, tartaric acid, succinic acid, maleic acid, and fumaric acid. A preferred buffer is citric acid.

Buffering agents useful with salts of the acidic drugs include, for example, tromethamine.

The optional pharmaceutically acceptable excipients assist in the manufacture of the novel formulations and include conventional materials such as lactose, magnesium stearate, talc, and sorbitol.

The novel formulation conveniently weighs about 50 to 1000 mg, for example 100 to 400 mg. The core comprises about 20 to 60%, and preferably about 30 to 60% by weight of polymer, the remainder being up to 50% of medicament, for example from 0.5 to 250 mg of active ingredient, and up to 10%, for example 2.5 to 100 mg of buffer plus inert excipients.

The ethylcellulose coating may conveniently be applied by spraying. The coat may comprise from 2 to 6% of core weight, preferably from 3 to 5%. This may typically represent a weight of coating of from 2 to 10 mg.

In use, the ethylcellulose coating layer of the product of this invention avoids the initial burst of release of medicament by providing an initial barrier to surface diffusion of medicament. Because the coating layer is water permeable, water and gastric fluid is able to permeate through the coating layer causing swelling of the core and dissolution of the medicament therein. During this initial period, usually approximately 1 - 2 hours, a small amount of medicament diffuses out at a slow rate, through the coating, hence providing the initial slow release.

As the gellation increases, the core expands until the coating material is ruptured. At this stage release is caused solely by diffusion from the gelled core matrix.

The formulations of the invention are illustrated by the following Examples. In the following Examples the medicament is the direct acting dopaminergic agent, (+)-trans-1a,2,3,4a,5,6-hexahydro-9-hydroxy-4-(1-propyl)-4H-naphth[1,2-b]-1,4-oxazine hydrochloride (I). Its use and the use of particular polymers, buffers, and inert additives and fillers in the particular amounts shown are not intended to limit the scope of this invention but are exemplary only. Other basic or acidic drugs and their salts, neutral or Zwitterionic compounds and other Polymers, buffers and inert additives and fillers with similar properties can be used.

All matrix formulations, independent of potency, were manufactured by the following general technique.

Compound I, HPMC K4M and lactose are mixed in a suitable blender. Citric acid is dissolved in a suitable volume of ethanol or water and added with mixing to the drug powders to obtain a suitable granular consistency. The mass is screened, dried, re-screened, lubricated with magnesium stearate and compressed on 10/32" (7.9 mm) punches.

EXAMPLE 1

Core Formulae and Their Release Characteristics

a)

Compound I	1.0 mg
Citric Acid	10 mg
HPMC K4M	80 mg
Lactose	108 mg
Magnesium stearate	1 mg
Total	200 mg

Time (hrs)	Cumulative % dose released at pH 1.2
2	46
4	63
6	81
8	90

b)

Compound I	5 mg
Citric Acid	10 mg
HPMC K4M	80 mg
Lactose	104 mg
Magnesium stearate	1 mg
Total	200 mg

Time (hrs)	Cumulative % dose released		
	pH 1.2	pH 5.5	pH 7.5
2	37	39	31
4	56	56	57
6	71	71	69
8	85	80	79
10	91	91	85

c)

Compound I	5 mg
Citric Acid	5 mg
HPMC K4M	80 mg
Lactose	109 mg
Magnesium stearate	1 mg
Total	200 mg

Time (hrs)	Cumulative % dose released	
	pH 1.2	pH 7.5
2	41	43
4	61	64
6	77	80
8	86	91
10	91	96

d)

Compound I	10 mg
Citric Acid	10 mg
HPMC K4M	80 mg
Lactose	99 mg
Magnesium stearate	1 mg
Total	200 mg

Time (hrs)	Cumulative % dose released
	pH 1.2
2	45
4	68
6	80
8	90

e)

Compound I	24 mg
Citric Acid	5 mg
HPMC K4M	80 mg
Lactose	90 mg
Magnesium stearate	1 mg
Total	200 mg

Time (hrs)	Cumulative % dose released	
	pH 1.2	pH 7.5
2	38	45
4	60	70
6	77	82
8	89	91
10	95	96

f) The Effect of Polymer Content on Release Characteristics

	HPMC content (% w/w)			
	20	30	40	60
Compound I	5 mg	5 mg	5 mg	5 mg
HPMC K4M	40 mg	60 mg	80 mg	120 mg
Lactose	144 mg	124 mg	104 mg	64 mg
Citric Acid	10 mg	10 mg	10 mg	10 mg
Magnesium Stearate	1 mg	1 mg	1 mg	1 mg
Total	200 mg	200 mg	200 mg	200 mg

Time (hrs)	Cumulative % dose released at pH 1.2			
	20%	30%	40%	60%
2	58	48	44	36
4	82	74	66	54
6	98	90	81	68
8	100	98	91	80
10	–	100	97	87

g) The Effect of Tablet Size on Release Characteristics

The composition described in Example 1.b) above was prepared and the granulation compressed at 100, 200 and 400 mg on 7/32"(5.6mm), 10/32"(7.9mm)and 13/32" (10.3mm)punches respectively.

Time (hrs)	Cumulative % dose released at pH 1.2		
	7/32"	10/32"	13/32"
2	48	40	37
4	74	60	56
6	87	79	71
8	91	89	82
10	94	95	90

EXAMPLE 2

Coating Formulae Applied to Cores

a) Core:

Compound I	5 mg
Citric Acid	10 mg
HPMC K4M	80 mg
Lactose	104 mg
Magnesium stearate	1 mg
Total	200 mg

The granule was prepared as described earlier and compressed on 5/16" (7.9 mm) concave punches.

Coating:

Aquacoat*	372 g
Dibutyl sebacate	28 g

* An aqueous dispersion of ethylcellulose containing 30% solids.

The suspension was prepared using conventional mixing equipment and applied to the tablets using the air-suspension method. A coat weight of 8 mg per tablet was applied.

Time (hrs)	Cumulative % dose released at pH 1.2
2	13
4	33
6	51
8	67
10	83
12	87

Release rate approximated to zero-order over the first 10 hours of the profile.

b) Core: As in Example 2(a) above.
Coating: Aquacoat 77 g
Myvacet 9-40 7 g
Water 78 g

Myvacet 9-40 is a distilled acetylated monoglyceride plasticiser available from Eastman Chemical Products of Tennessee, U.S.A.

The coating procedure was as described above. A theoretical coat weight of 4 mg per tablet was applied.

Time (hrs)	Cumulative % dose released		
	pH 1.2	pH 5.5	pH 7.5
2	25	26	39
4	41	49	62
6	62	67	76
8	77	81	85
10	87	92	90
12	93	100	92

The pH dependence has little in vivo significance and is a function of the pH solubility profile of the coat. Under in vivo conditions release will initiate shortly after ingestion at about pH 1 and the "burst effect" will consequently be eliminated. A pH of 7-7.5 will not be achieved until 4 to 5 hours after dosing and if the rates are examined after this period they are seen to be essentially independent of pH.

c) The Effect of Matrix Polymer content on Release Characteristics of Coated Tablets

Core Formulae: As in Example 1(f) above
Coating: As in Example 2(b) above

The coating procedure was as described above. A theoretical coat weight of 5.5 mg tablet was applied.

	Cumulative % dose released at pH 1.2 HPMC Content (% w/w)		
Time/Hrs	30%	40%	60%
2	12.3	25.4	26.6
4	-	40.9	-
6	-	62.2	-
8	-	77.2	-
10	83.7	86.5	81.0
12	92.1	92.7	88.6

Flexibility in modifying the release profile can be achieved by altering the polymer contents of the tablet core and coat.

Claims

Claims for the following Contracting States : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. A sustained release pharmaceutical composition in oral dosage form comprising: (1) a core matrix containing at least 20% of a derivatized cellulosic gelling agent, a medicament homogeneously dispersed therein and optionally pharmaceutically acceptable excipients; and (2) a coating layer surrounding the core matrix; characterised in that the material used for the coating layer is ethylcellulose.

2. The composition of Claim 1 wherein the core matrix contains a buffering agent.

3. The composition of Claim 2 wherein the buffering agent is citric acid.

4. The composition of any one of Claims 1 to 3 wherein the core matrix gelling agent is hydroxypropylmethylcellulose.

5. The composition of Claim 4 wherein the hydroxypropylmethylcellulose has a viscosity of about 400 $kgm^{-1}s^{-1}$ (4,000 centipoises).

6. The composition of any one of Claims 1 to 5 wherein the medicament is (+)-trans-1a,2,3,4a,5,6-hexahydro-9-hydroxy-4-(1-propyl)-4H-naphth[1,2-b]-1,4-oxazine hydrochloride.

7. A method of preparing a sustained release pharmaceutical composition in oral dosage form containing an active ingredient which comprises forming a matrix containing at least 20% of a derivatized cellulosic gelling agent having said active ingredient homogeneously dispersed therein optionally together with pharmaceutically acceptable excipients, and forming a coating on said matrix; characterised in that the material used for forming the coating is ethylcellulose.

Claims for the following Contracting States : AT, ES, GR

1. A method of preparing a sustained release pharmaceutical composition in oral dosage form containing an active ingredient which comprises forming a matrix containing at least 20% of a derivatized cellulosic gelling agent having said active ingredient homogeneously dispersed therein optionally together with pharmaceutically acceptable excipients, and forming a coating on said matrix; characterised in that the material used for forming the coating is ethylcellulose.

2. The method of Claim 1 wherein the core matrix contains a buffering agent.

3. The method of Claim 2 wherein the buffering agent is citric acid.

4. The method of any one of Claims 1 to 3 wherein the core matrix gelling agent is hydroxypropylmethylcellulose.

5. The method of Claim 4 wherein the hydroxypropylmethylcellulose has a viscosity of about 400 $kgm^{-1}s^{-1}$ (4,000 centipoises).

6. The method of any one of Claims 1 to 5 wherein the medicament is (+)-trans-1a,2,3,4a,5,6-hexahydro-9-hydroxy-4-(1-propyl)-4H-naphth[1,2-b]-1,4-oxazine hydrochloride.

Revendications

Revendication pour les Etats contractants suivants : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Composition pharmaceutique à libération prolongée sous forme d'une dose d'administration orale, comprenant : (1) une matrice centrale, contenant au moins 20 % d'un agent gélifiant qui est un dérivé de la cellulose, où un médicament est dispersé de façon homogène, et facultativement des excipients pharmaceutiquement acceptables ; et (2) une couche d'enrobage entourant la matrice centrale, caractérisée en ce que la matière utilisée pour la couche d'enrobage est l'éthylcellulose.

2. Composition selon la revendication 1, dans laquelle la matrice centrale contient un agent tampon.

3. Composition selon la revendication 2, dans laquelle l'agent tampon est l'acide citrique.

4. Composition selon l'une quelconque des revendications 1 à 3, dans laquelle l'agant gélifiant de la matrice centrale est l'hydroxyméthylpropylcellulose.

5. Composition selon la revendication 4, dans laquelle l'hydroxyméthylpropylcellulose a une viscosité d'environ 400 $kgm^{-1}s^{-1}$ (4 000 centipoises).

6. Composition selon l'une quelconque des revendications 1 à 5, dans laquelle le médicament est le chlorhydrate de (+)-trans-1a,2,3,4a,5,6-hexahydro-9-hydroxy-4-(1-propyl)-4H-napht[1,2-b]-1,4-oxazine.

7. Procédé pour préparer une composition pharmaceutique à libération prolongée sous forme d'une dose d'administration orale contenant un ingrédient actif, qui consiste à former une matrice contenant au moins 20% d'un agent gélifiant qui est un dérivé de la cellulose, dans laquelle ledit ingrédient actif est dispersé de façon homogène, facultativement avec des excipients pharmaceutiquement acceptables, et former un enrobage sur ladite matrice ; caractérisé en ce que la matière utilisée pour former l'enrobage est l'éthylcellulose.

Revendication pour les Etats contractants suivants : AT, ES, GR

1. Procédé pour préparer une composition pharmaceutique à libération prolongée sous forme d'une dose d'administration orale contenant un ingrédient actif, qui consiste à former une matrice, contenant au moins 20 % d'un agent gélifiant qui est un dérivé de la cellulose, dans laquelle ledit ingrédient actif est dispersé de façon homogène, facultativement avec des excipients pharmaceutiquement acceptables, et former un enrobage sur ladite matrice ; caractérisé en ce que la matière utilisée pour former l'enrobage est l'éthylcellulose.

2. Procédé selon la revendication 1, dans lequel la matrice centrale contient un agent tampon.

3. Procédé selon la revendication 2, dans lequel l'agent tampon est l'acide citrique.

4. Procédé selon l'une quelconque des revendications 1 à 3, dans lequel l'agent gélifiant de la matrice centrale est l'hydroxypropylméthylcellulose.

5. Procédé selon la revendication 4, dans lequel l'hydroxypropylméthylcellulose a une viscosité d'environ 400 $kgm^{-1}s^{-1}$ (4 000 centipoises).

6. Procédé selon l'une quelconque des revendications 1 à 5, dans lequel le médicament est le

chlorhydrate de (+)-trans-1a,2,3,4a,5,6-hexahydro-9-hydroxy-4-(1-propyl)-4H-napht[1,2-b]-1,4-oxazine.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Pharmazeutische Zusammensetzung mit verzögerter Freisetzung in oraler Dosierungsform, welche umfaßt: (1) eine Kernmatrix, die wenigstens 20 % eines derivatisierten Cellulose-Gelierungsmittels, ein homogen darin dispergiertes Medikament und gegebenenfalls pharmazeutisch annehmbare Exzipienten enthält und (2) eine die Kernmatrix umgebende Überzugsschicht, dadurch gekennzeichnet, daß das für die Überzugsschicht verwandte Material Ethylcellulose ist.

2. Zusammensetzung nach Anspruch 1, worin die Kernmatrix ein Puffermittel enthält.

3. Zusammensetzung nach Anspruch 2, worin das Puffermittel Citronensäure ist.

4. Zusammensetzung nach einem der Ansprüche 1 bis 3, worin das Gelierungsmittel der Kernmatrix Hydroxypropylmethylcellulose ist.

5. Zusammensetzung nach Anspruch 4, worin die Hydroxypropylmethylcellulose eine Viskosität von etwa 400 $kgm^{-1}s^{-1}$ (4000 Centipoises) hat.

6. Zusammensetzung nach einem der Ansprüche 1 bis 5, worin das Medikament (+)-trans-1a,2,3,4a,5,6-Hexahydro-9-hydroxy-4-(1-propyl)-4H-naphth[1,2-b]-1,4-oxazinhydrochlorid ist.

7. Verfahren zur Herstellung einer pharmazeutischen Zusammensetzung mit verzögerter Freisetzung in oraler Dosisform, die einen Wirkstoff enthält, durch Bilden einer Matrix, die wenigstens 20 % eines derivatisierten Cellulose-Gelierungsmittels mit dem homogen darin dispergierten Wirkstoff, gegebenenfalls zusammen mit pharmazeutisch annehmbaren Exzipienten, enthält, und Bilden eines Überzugs auf dieser Matrix, dadurch gekennzeichnet, daß das für die Bildung des Überzugs verwandte Material Ethylcellulose ist.

Patentansprüche für folgende Vertragsstaaten : AT, ES, GR

1. Verfahren zur Herstellung einer pharmazeutischen ZusammenSetzung mit verzögerter Freisetzung in oraler Dosisform, die einen Wirkstoff enthält, durch Bilden einer Matrix, die wenigstens 20 % eines derivatisierten Cellulose-Gelierungsmittels mit dem homogenen darin dispergierten Wirkstoff, gegebenenfalls zusammen mit pharmazeutisch annehmbaren Exzipientien, enthält, und Bilden eines Überzugs auf dieser Matrix, dadurch gekennzeichnet, daß das für die Bildungdes Überzugs verwandte Material Ethylcellulose ist.

2. Verfahren nach Anspruch 1, worin die Kernmatrix ein Puffermittel enthält.

3. Verfahren nach Anspruch 2, worin das Puffermittel Citronensäure ist.

4. Verfahren nach einem der Ansprüche 1 bis 3, worin das Kernmatrix-Gelierungsmittel Hydroxypropylmethylcellulose ist.

5. Verfahren nach Anspruch 4, worin die Hydroxypropylmethylcellulose eine Viskosität von etwa 400 $kgm^{-1}s^{-1}$ (4 000 Centipoises) hat.

6. Verfahren nach einem der Ansprüche 1 bis 5, worin das Medikament (+)-trans-1a,2,3,4a,5,6-Hexahydro-9-hydroxy-4-(1-propyl)-4H-naphth[1,2-b]-1,4-oxazinhydrochlorid ist.